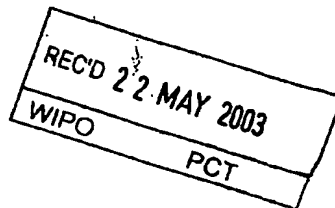


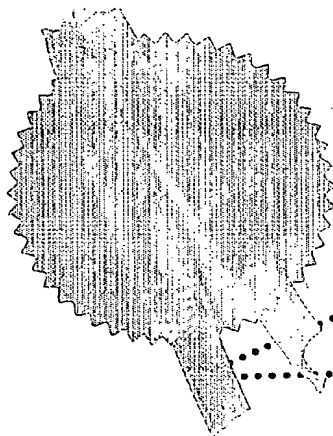
PCT / I N O 3 / 0 0 0 0 6

THE PATENTS ACT, 1970



IT IS HEREBY CERTIFIED THAT, the annex is a true copy of
Application and Complete specification filed on 07.01.2002 in respect
of Patent Application No. 10/MUM/2002 of Sun Pharmaceutical
Industries Ltd, Acme Plaza, Andheri-Kurla Road, Andheri (E)
Mumbai-400 059, India, an Indian Company.

This certificate is issued under the powers vested on me under
Section 147(1) of the Patents Act, 1970.....



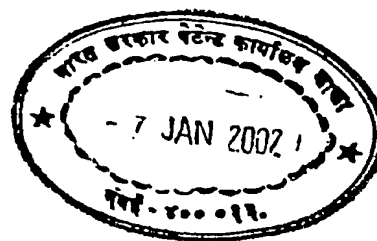
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RULE 17.1(a) OR (b)

Dated this 10th day of February 2003

N.K. GARG
(N.K. GARG)

ASST CONTROLLER OF PATENTS & DESIGNS

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FORM 1

THE PATENTS ACT, 1970
(39 OF 1970)

APPLICATION FOR GRANT OF A PATENT
(See sections 5(2), 7, 54 and 135 and rule 33A)

We, **SUN PHARMACEUTICAL INDUSTRIES LTD., ACME PLAZA, ANDHERI-KURLA ROAD, ANDHERI (E), MUMBAI-400059, INDIA**

AN INDIAN COMPANY

hereby declare -

- (i) that we are in possession of an invention titled "**PROCESS FOR THE PREPARATION OF CRUDE 1-[3-(DIMETHYLAMINO) PROPYL]-1-(4-FLUOROPHENYL)-1,3-DIHYDRO-5-ISOBENZOFURAN CARBONITRILE BASE**"
- (ii) that the complete specification relating to this invention is filed with this application.
- (iii) that there is no lawful ground of objection to the grant of a patent to us.

We, further declare that the inventors for the said invention are

1) Mr. Patel Nileshkumar Sureshbhai 2) Dr. Kilaru Srinivasu
3) Dr. Chinnapillai Rajendran 4) Dr. Thennati Rajamannar : of **SUN PHARMA ADVANCED RESEARCH CENTRE, AKOTA ROAD, AKOTA, BARODA 390020, GUJARAT, INDIA; an Indian national.**

We claim the priority from the applications filed in convention countries, particulars of which are as follows: Not Applicable

We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which we are the applicant: Not Applicable

We state that the application is divided out of our application, the particular of which are given below and pray that this application deemed to have been filed under section 16 of the Act: Not Applicable

That we are the assignee of the true and first inventors.

That our address for service in India is as follows-

Dr. RATNESH SHIVASTAVA,
INTELLECTUAL PROPERTY CELL,
SUN PHARMACEUTICAL INDUSTRIES LTD,
ACME PLAZA, ANDHERI-KURLA ROAD,
ANDHERI (E), MUMBAI-400 059, INDIA,
TELEPHONE NO-8397632, FACSIMILE NO- 8212110.

TRIPPLICATE

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MUM

7 JAN 2002

Following declaration was given by the inventors-
We, the true and first inventors for this invention declare that the applicant herein is our assignee.

Dated this 3rd day of January, 2002.

(Signatures)

1. _____
Mr. Patel Nileshkumar Sureshbhai

2. _____
Dr. Kilaru Srinivasu

3. _____
Dr. Chinnapillai Rajendran

4. _____
Dr. Thennati Rajamannar

That to the best of our knowledge, information and belief, the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of a patent to us on this application.

Following are the attachment with the application:

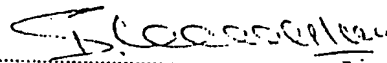
- 1) Complete specification (3 copies)
- 2) Fee Rs. 5000 in cheque bearing No. 186610 dated 26.12.01 on Bank of Baroda.

We request that a patent may be granted to us for the said invention

Dated this 4th day of January, 2002.

X

(Signature)



DILIP SHANGHVI
CHAIRMAN AND MANAGING DIRECTOR
SUN PHARMACEUTICAL INDUSTRIES LTD.

To

The Controller of Patents,
The Patent Office,
Mumbai - 400 013.

FORM 2

THE PATENTS ACT, 1970
(39 OF 1970)

COMPLETE SPECIFICATION
(See section 10)

PROCESS FOR THE PREPARATION OF CRUDE 1-[3-(DIMETHYLAMINO) PROPYL]-1-(4-FLUOROPHENYL)-1,3-DIHYDRO-5-ISOBENZOFURAN CARBONITRILE BASE

SUN PHARMACEUTICAL INDUSTRIES LTD.

A company incorporated under the laws of India having their office at ACME
PLAZA, ANDHERI-KURLA ROAD, ANDHERI (E), MUMBAI-400059.
MAHARASHTRA, INDIA

TRIPPLICATE

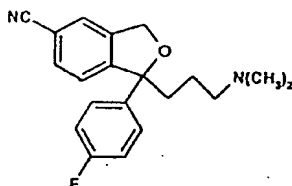
The following specification particularly describes and ascertains the
nature of this invention and the manner in which it is to be performed.

10 | मुंबई | 2002
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17 JAN 2002

PROCESS FOR THE PREPARATION OF CRUDE 1-[3-(DIMETHYLAMINO) PROPYL]-1-(4-FLUOROPHENYL)-1,3-DIHYDRO-5-ISOBENZOFURAN CARBONITRILE BASE

This invention provides a process for the preparation of crude 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base with substantially low levels of impurities. 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile, commonly known as citalopram (INN Name) is a compound of **Formula I**. 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base with substantially low levels of impurities is useful in obtaining salts of 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile, in particular, 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile hydrobromide of pharmaceutical quality by a simple process. 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile hydrobromide is a well known antidepressant.

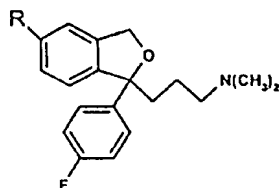


Formula I

PRIOR ART:

United States Patent No.4,136,193 (Indian reference not available, hereinafter referred to as '193) claims 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile or its pharmaceutically acceptable acid addition salt. It discloses a process for the preparation of 1-[3-(dimethylamino) propyl]-1-(4-

fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile from the penultimate 5-substituted derivatives, compounds of **Formula II** wherein R is halogen or trifluoromethyl, by reaction with cyanide source.



Formula II

The exchange process described for the preparation of 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile gives the desmethylcitalopram and other high molecular weight impurities in unacceptable amounts. Purifying such an impure material makes the process economically unviable.

United Kingdom patent No. GB 2356199 (Indian reference not available) included examples wherein 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile crude base was prepared by the cyanide exchange process but with sulfolane as a solvent, instead of dimethylformamide as reported in '193. It is disclosed in the patent that the cyanide exchange process of '193 patent results in formation of high molecular weight impurities including dimeric reaction products in unacceptable amounts. The use of film distillation process was made to obtain higher purity 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base. The patent claims this process with additional purification steps that are required.

PCT publication WO 0011926 discloses the conversion of compound of **Formula II** wherein R maybe Cl or Br to 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-

dihydro-5-isobenzofuran carbonitrile or its pharmaceutically acceptable salt with a cyanide source in the presence of a nickel catalyst. The process was stated to result in 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile in high yield as a very pure product.

PCT publication WO 0013648 discloses the conversion of compound of Formula II wherein R maybe bromo or iodo to 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile or its pharmaceutically acceptable salt with a cyanide source in the presence of a palladium catalyst which is expensive.

PCT publication WO 0102383 discloses the synthesis of 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile by reaction of compound of Formula II wherein R is a halogen atom, preferably bromine with activated magnesium to form the Grignard reagent followed by reaction of the Grignard with a compound containing a -CN group bound to a leaving group. The reported process enables 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile in high yields.

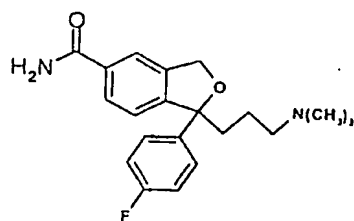
PCT publication WO 0145483 discloses the cyanide exchange reaction of compound of Formula II wherein R maybe iodo, bromo, chloro or $\text{CF}_3\text{-(CF}_2\text{)}_n\text{-SO}_2\text{-O-}$, n-being 0,1,2,3,4,5,6,7, or 8 to give 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile or its pharmaceutically acceptable salt with a cyanide source. The crude 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base has a purity of about 85% which is optionally subjected to some initial purification and treatment with an amide or an amide-like forming agent, acid/base wash and/or crystallization and recrystallization of 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile in order to remove the amides formed and the resulting 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile product is optionally further purified, worked up and isolated as the base or pharmaceutically acceptable salt thereof. This process involves a laborious work-

up procedure to obtain high purity 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile.

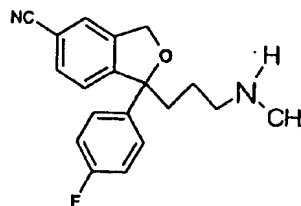
Several other patents report the preparation of 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile with different starting materials viz.

1. Conversion of 5-amido or ester group to a 5-cyano group (WO 9819513)
2. Conversion of 5-amino group to a 5-cyano group (WO 9819512)
3. Conversion of 5-formyl group to a 5-cyano group (WO9930548)
4. Conversion of 5-oxazoliny or thiazoliny group to 5-cyano group (WO 0023431)
5. Conversion of 5-substituted groups like R_1R_2N-CO- or 4,5-dihydro-1,3-oxazol-2-yl optionally substituted in the 4- and or 5-position with one or more alkyl, aryl or heteroaryl groups to the 5-cyano group (WO 9930548)

The major impurities that are formed when the cyanide exchange process as disclosed in '193 patent is followed are 5-carboxamide -1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-phthalide, a compound of **Formula III**, and desmethylcitalopram, a compound of **Formula IV**, along with unconverted starting material. The process described in the '193 patent involves refluxing the reaction mixture in DMF for 4 hours followed by isolation of product to get the crude base. However, under these conditions we observed the presence of 10-25% of starting material along with amide and descitalopram as impurities and found it extremely difficult to purify the product to the desired levels. Even when the reaction was continued for several hours (>15 hours) the unreacted starting material remained in the range of 0.5 to 5 % and purity of the desired product decreased to about 60%. It was observed that high molecular weight impurities were formed. The formation of these impurities increased with increase in duration of reaction time to values as high as 20%. These impurities were difficult to remove by usual work up procedure leading to extensive and expensive purification process.



Formula III



Formula IV

OBJECTIVES OF THE INVENTION

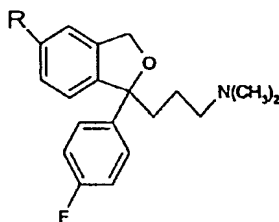
The objective of the present invention is to provide crude 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base with substantially low levels of impurities and thus avoid an extensive and expensive purification process.

It is a further objective of the present invention to arrest the formation of substantial amount of carboxamide impurity, high molecular weight impurities and to suppress desmethylcitalopram besides taking the cyanide exchange reaction to nearing completion so as to obtain crude 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base in substantially high purity.

A simple process for the preparation of crude 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base with low level of impurities has been found. The process avoids the extensive work-up of the prior art processes.

SUMMARY OF THE INVENTION

The present invention provides a process for the preparation of crude 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base with substantially low levels of impurities, the process comprising reacting a compound of the Formula II



Formula II

wherein R is Cl or Br with a cyanide source in presence of an iodide and a non polar aprotic solvent.

The process of the present invention provides crude 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base with substantially low levels of impurities.

According to the process of the present invention the cyanide source may be selected from KCN, NaCN, CuCN; [(R')₄N] CN where (R')₄ indicates four groups which may be the same or different selected from hydrogen and straight chain or branched alkyl, and the like, preferably KCN, NaCN and CuCN, the most preferred being CuCN.

According to the process of the present invention the iodides that may be used in the present invention are selected from stable metal iodides, alkali and alkaline earth metal iodides.

According to the process of the present invention the preferred iodides being alkali and alkaline earth metal iodides and the most preferred being alkali metal iodides like potassium iodide.

According to the process of the present invention the preferred iodide is employed is in the mole ratio of 0.1-10 moles preferably 1-5 moles, the most preferred being 1-3 moles.

According to the process of the present invention the non polar aprotic solvent may be selected from the group of amides, amines and polyethers.

According to the process of the present invention the amide solvents may be selected from N,N-dialkyl, N-alkyl,N'-aryl, N,N-Diaryl, formamides, akylamides, arylamides and N-alkyl lactams; such as dimethyl formamide, dimethyl acetamide, N-methyl,N'-Phenyl formamide, N-Methyl,N'-phenyl acetamide, N-methylpyrrolidone etc, preferably amide solvents having boiling point $>100^{\circ}\text{C}$.

According to the process of the present invention the amine solvents may be selected from aliphatic amines, cyclic amines, acyclic amines of primary, secondary and tertiary nature and aromatic amines like isoquinolines, quinolines, dialkylarylamines, pyridine and substituted pyridines. The preferred amine bases are aliphatic, cyclic or acyclic tertiary amines, pyridine and substituted pyridine bases such as lutidine. The most preferred being the pyridine and substituted pyridine bases. The substituted pyridines are symmetrical polyalkyl substituted, unsymmetrical polyalkyl sbstituted and dimethylamino pyridine like bases.

According to the process of the present invention the polyether solvents may be selected from polyethyleneglycols, diarylethers, alkylarylethers etc. The preferred being polyethyleneglycols and diaryl ethers and the most preferred being polyethyleneglycol with a molecular weight range of 200-10,000.

The solvents viz. amides, amine bases and ethers can be used as a mixture in the range of 1-99% or as neat solvents, the most preferred being as neat solvent.

According to the process of the present invention the reaction is carried out in presence of potassium iodide and the most preferred solvent pyridine.

According to the process of the present invention the reaction is carried out at a temperature between 100 - 200°C for 10 - 30 hours, the preferred being 120 -160°C for 20-30 hours and the most preferred being 130-150°C for 20 - 28 hours.

The invention is illustrated but not restricted by the description in the following examples.

EXAMPLES

COMPARATIVE EXAMPLE 1

This example illustrates the preparation of 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile according to the prior art (United States Patent No.4,136,193)

5-bromo-1—(4-fluorophenyl)-1-(3-dimethylaminopropane)- phthalane (50.0 g) and Copper (I) cyanide (13.0 g) in 36 millilitres of dimethylformamide is refluxed and worked up to obtain the crude 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base with the HPLC profile as given in Table I & II.

COMPARATIVE EXAMPLE 2

This example illustrates the preparation of 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile according to the prior art (United States Patent No.4,136,193)

5-bromo-1—(4-fluorophenyl)-1-(3-dimethylaminopropane)- phthalane (25.0 g) and Copper (I) cyanide (6.5 g) in 18 millilitres of dimethylformamide is refluxed and worked up to obtain the crude 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base with the HPLC profile as given in Table I & II.

Example 1

Potassium iodide (100g), Copper (I) cyanide (48.5g) are added to a solution of the 5-bromo-1-(4-fluorophenyl)-1-(3-dimethylaminopropane)-phthalane (100g) in pyridine (100ml). The reaction mixture is heated to 135-145°C and maintained for 28 hours. The reaction mixture is cooled to 100°C and poured in ammonia solution containing toluene stirred for 2 hours to get a clear separation of layers. Then the organic layer after acid base treatment is separated and washed with water twice (2x300ml) and dried with anhydrous sodium sulfate. The toluene layer is distilled to get the crude 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base 74 gm with the following HPLC profile.

Starting material 0.79%, Desmethyl impurity 0.15%, amide impurity 0.6%, higher retention time impurities <0.1% and 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile 94.4%.

Example 2

Potassium iodide (45g), Copper (I) cyanide (21g) are added to a solution of the 5-bromo-1-(4-fluorophenyl)-1-(3-dimethylaminopropane)-phthalane (45g.) in pyridine (45ml) and PEG-400 (45ml). The reaction mixture is heated to 135-145°C and maintained for 27 hours. The reaction mixture is cooled to 100°C poured in to ammonia solution containing toluene and stirred for 2 hours to get a clear separation of layers. Then the organic layer after acid base treatment is separated and washed with water twice (2x100ml), dried with anhydrous sodium sulfate. The toluene layer is distilled to get the crude 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base 35.5 gm with the following HPLC profile.

Starting material 1.01%, Desmethyl impurity 0.18%, amide impurity 0.47%, higher retention time impurities <0.1% and 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile 92.3%.

TABLE I : HPLC profile of reaction mass

Comp. Example	After 4 hrs				After 10 hrs				After 15 hrs				After 20 hrs			
	Product	S.M	Amide	N-des	Purity	S.M	Amide	N-des	Purity	S.M	Amide	N-des	Purity	S.M	Amide	N-des
1	77.8	10.9	0.45	0.9	73.5	2.12	0.66	6.7	71.7	2.6	0.9	4.6	67.5	2.8	2.6	1.2
2	71.7	18.0	1.48	0.59	77.7	6.8	1.7	1.4	74.8	3.9	3.1	2.4	56.4	0.5	7.1	6.3

TABLE II: High Molecular Weight Compounds (which clute at higher Retention Times)

Comp. Example	After 4 hrs				After 10 hrs				After 15 hrs				After 20 hrs			
	RT	26.1	28.5	30.4	RT	26.1	28.4	30.4	RT	26.4	28.7	30.7	RT	26.3	28.5	30.5
1	Area %	-	0.24	2.35	Area %	0.07	2.07	4.44	Area %	0.23	3.16	6.2	Area %	0.2	6.6	11.03
2	RT		30.6	33.4	RT	28.7	30.6	33.4	RT	28.8	30.7	33.5	RT	28.7	30.6	33.5
	Area %	-	0.64	0.07	Area %	0.38	3.07	0.1	Area %	0.95	4.56	0.1	Area %	3.4	13.5	-

Product 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile

S.M. Starting material i.e. 5-bromo-1-(4-fluorophenyl)-1-(3-dimethylaminopropane)- phthalane

Amide 5-carboxamide -1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-phthalide

N-des Desmethylcitalopram

Example 3

Potassium iodide (25g), Copper (I) cyanide (9.7g) are added to a solution of the 5-bromo-1—(4-fluorophenyl)-1-(3-dimethylaminopropane)-phthalane (25g) in 2,6-lutidine(25ml) and dimethylformamide (25ml). The reaction mixture is heated to 135-145°C and maintained for 24 hours. The reaction mixture is cooled to 100°C and poured in to ammonia solution containing toluene stirred for 2 hours to get a clear separation of layers. Then the organic layer after acid base treatment is separated and washed with water twice (2x100ml), dried with anhydrous sodium sulfate and finally the toluene layer is distilled to get the crude 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base 17.5gm with the following HPLC purofile.

Starting material 4.39%, Desmethyl impurity 0.2%, amide impurity 0.45%, higher retention time impurities <0.1% and 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile 93.0%.

Example 4

Potassium iodide (25g), Copper (I) cyanide (11.8g,) are added to a solution of the 5-bromo-1—(4-fluorophenyl)-1-(3-dimethylaminopropane)- phthalane (25g) in PEG-400 (25 ml). The reaction mixture is heated to 135-145°C and maintained for 28 hours. The reaction mixture is cooled to 100°C and poured in ammonia solution containing toluene stirred for 2 hours to get a clear separation of layers. Then the organic layer after acid base treatment is separated and washed with water twice (2x100ml) and dried with anhydrous sodium sulfate. The toluene layer is distilled to get the crude 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base 18 gm with the following HPLC profile.

Starting material 4.9%, Desmethyl impurity 0.54%, amide impurity 2.74%, higher retention time impurities not observed and 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile 85.1%.

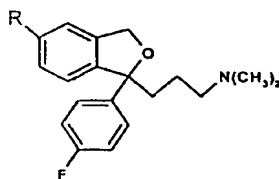
Example 5

Potassium iodide (25g), Copper (I) cyanide (11.8g) are added to a solution of the 5-bromo-1-(4-fluorophenyl)-1-(3-dimethylaminopropane)-phthalane (25g) in dimethylformamide (25ml). The reaction mixture is heated to 135-145°C and maintained for 28 hours. The reaction mixture is cooled to 100°C and poured in ammonia solution containing toluene and stirred for 2 hours to get a clear separation of layers. Then the organic layer after acid base treatment is separated and washed with water twice (2x100ml), dried with anhydrous sodium sulfate and finally the toluene layer is distilled to get the crude 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base 16.5gm with the following HPLC profile.

Starting material 1.91%, Desmethyl impurity 0.36%, amide impurity 8.4%, higher retention time impurities <0.1% and 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile 80.4%.

We claim:

1. A process for the preparation of crude 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base with substantially low levels of impurities, the process comprising reacting a compound of Formula II



Formula II

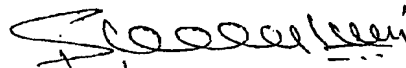
wherein R is Cl or Br with a cyanide source in presence of an iodide and a non polar aprotic solvent.

2. A process as claimed in claim 1 wherein the cyanide source is selected from KCN, NaCN, CuCN and [(R')₄N] CN where (R')₄ indicates four groups which may be the same or different selected from hydrogen and straight chain or branched alkyl.
3. A process as claimed in claim 2 wherein the cyanide source is CuCN.
4. A process as claimed in claim 1 wherein the iodide is selected from the group of stable metal iodides, alkali and alkaline earth metal iodides.
5. A process as claimed in claim 4 wherein the iodide is potassium iodide.
6. A process as claimed in claim 1 wherein the solvent is selected from the group of amides, amines and polyethers.

7. A process as claimed in claim 6 wherein the solvent is pyridine.
8. A process as claimed in claim 6 wherein the solvent is lutidine.
9. A process as claimed in claim 1 wherein the reaction is carried out at a temperature between 100 – 200°C for 10-30 hours.
10. A process as claimed in claim 9 wherein the reaction is carried out at a temperature between 130 – 150°C for 20-28 hours.
11. A process as claimed in claims 1 to 8 substantially as herein described and illustrated by examples 1 to 5.

Dated this 4th day of January, 2002.

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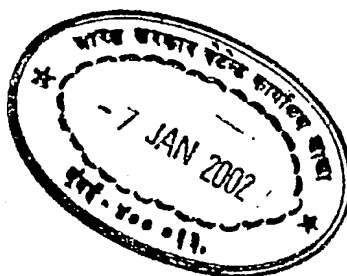
DILIP SHANGHVI
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ABSTRACT

The present invention provides a process for the preparation of crude 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base with substantially low levels of impurities by arresting the formation of substantial amount of carboxamide impurity, high molecular weight impurities and suppressing the formation of desmethylcitalopram besides taking the cyanide exchange reaction to near completion and thus avoiding an extensive and expensive purification process.

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